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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/648,389	08/25/2000	David Pinsky	62683/JPW/JML	5890

7590 01/09/2003

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/09/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/648,389	PINSKY ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7 and 9-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7 and 9-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

Applicant's Amendment filed October 2, 2002 in Paper No. 11 is acknowledged. Claims 2, 4, 6 and 8 have been canceled. Claim 3 has been amended. A paper copy of the sequence listing and a computer disk containing the CRF of the sequence listing is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 5, 7 and 9-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for reducing vascular injury during reperfusion of an ischemia-induced lung tissue, which comprises contacting the tissue with a nucleic acid of the sequence of SEQ ID NO: 1, which inhibits (antisense) Egr-1 before, during or after reperfusion, does not reasonably provide enablement for a method for reducing vascular injury during reperfusion of an ischemic tissue wherein the tissue is to be transplanted into a subject; wherein the tissue is a heart, a vein, an artery, a stomach, a colon, a liver, skin, an eye, a pancreas, a brain, a finger, a toe or a limb; wherein the subject has suffered a stroke, or a myocardial infarction; wherein the subject is undergoing angioplasty, cardiac surgery, vascular surgery, or organ transplantation; wherein the vascular surgery is coronary artery surgery. This

rejection is maintained for the reasons of record for rejection of claims 1, 3, 5, 7 and 9-27, as set forth in the Office action mailed July 3, 2002 in Paper No. 10.

1. Applicant's traversal and request for reconsideration and withdrawal of the 35 U.S.C. 112, first paragraph rejection against claims 1, 3, 5, 7 and 9-27 has been fully considered. Applicants argue that the specification is enabled such that one of ordinary skill in the art could make and use the claimed invention. More specifically, applicants argue that the specification clearly teaches the role of Egr-1 in ischemia/reperfusion in a model of ischemic tissue and a method for reducing damage to an ischemic tissue by contacting an ischemic tissue with an inhibitor of Egr-1. Applicants direct the Examiner to data recited in Figures 5A, 13 and the specification to support of the role of Egr-1 in ischemia/reperfusion.

Applicant's arguments have been fully considered but they are not found persuasive. As stated in the previous Office Action, filed in Paper No. 10, delivery of antisense oligonucleotide to the target organ, cell and intracellular location in quantities sufficient to inhibit specific gene expression is unpredictable (see Branch). The cited reference indicates that it is unpredictable whether the quantity of antisense oligonucleotide delivered to the intracellular will be sufficient to specifically interfere with gene expression. Furthermore, the design of antisense oligonucleotides that inhibit gene expression *in vivo* requires trial and error experimentation. Branch also states that the relationship between accessibility to oligonucleotide (ODN) binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored...It is not yet clear whether *in vitro* screening techniques...will identify ODN's that are effective *in vivo*.

The previous Office Action, filed in Paper No. 10 also demonstrates the unpredictability of antisense oligonucleotides as therapeutics by Jen et al. who discuss antisense-based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. The previous Office Action, filed in Paper No. 10, states, "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." (see Jen et al.).

Rosenberg et al. [U.S. Patent No: 5,593,974] also demonstrate the unpredictability of antisense-based therapeutics. Rosenberg et al. state, "while antisense oligonucleotides have been shown to be capable of interfering selectively with protein synthesis, and significant progress has been made on improving their intracellular stability, the problem remains that oligonucleotides must reach their intended intracellular site of action in the body in order to be effective. Where the intended therapeutic effect is a systemic one, oligonucleotides may be administered systemically. However, when it is necessary or desirable to administer the oligonucleotide to a specific region within the body, systemic administration typically will be unsatisfactory" (see column 2, lines 5-15).

In view of the unpredictability of antisense nucleic acids as therapeutics, trial and error experimentation would be required of a person of skill in the art to devise a method for reducing damage to an ischemic tissue which comprises contacting cells of the tissue with an inhibitor of Egr-1. Furthermore, in view of the unpredictability of antisense nucleic acids as therapeutics, trial and error experimentation would be required of a person of skill in the art to devise a method for reducing vascular injury during reperfusion of an ischemic tissue in a subject which

comprises contacting the tissue with a compound which inhibits expression of Egr-1 protein in the tissue so as to reduce vascular injury in the tissue during reperfusion.

As stated in the previous Office Action, filed in Paper No. 10, the quantity of experimentation required would include the testing of ischemic tissues from different lineages (e.g. stomach, or eye, or brain), the degree of ischemia (e.g. moderate or extreme) and the variability in contact time that would result in the reduced damage to the ischemic tissue. The amount of experimentation would also include overcoming the obstacles to routine antisense therapies as exemplified in the references discussed in Branch, Jen et al. and Rosenberg et al.

This rejection is maintained for the reasons of record for rejection of claims 1, 3, 5, 7 and 9-27, as set forth in the Office action mailed July 3, 2002 in Paper No. 10.

2. Applicant's traversal and request for reconsideration and withdrawal of the 35 U.S.C. 102(b) rejection against claims 1-9, 11, 15 and 26 has been fully considered, is found persuasive and is hereby withdrawn.

Examiner agrees that the *in vitro* **mechanical injury** model of Santiago et al. does not encompass the method for **reducing damage to an ischemic tissue** with an inhibitor of Egr-1 of the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 5, 7 and 9-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 5, 7 and 9-27 recite the term "ischemic tissue". The term "ischemic tissue" in claims 7, 3, 5, 7 and 9-27 is a relative term which renders the claims indefinite. The term "ischemic tissue" is not defined by the claims and the specification does not provide a standard for ascertaining the requisite degree, and one of skill in the art would not be reasonably apprised of the scope of the invention. The specification at page 14, paragraph 2, defines, "ischemic disorder". However, the specification does not provide a standard for ascertaining an "ischemic tissue". Clarification is required.

Conclusion

Claims 1, 3, 5, 7 and 9-27 remain rejected.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-8693 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
January 6, 2003

SEAN McGARRY
PRIMARY EXAMINER